

Applicant : Verlan H. VanRheenen  
Appln. No. : 10/815,351  
Page : 3

### REMARKS

The specification has been amended to overcome an objection regarding chart A at page 5 of the specification. None of the claims have been amended. Accordingly, claims 1-4 remain pending and under consideration in the application.

#### Telephonic Interview

During a telephonic interview with Examiner Barbara P. Badio, Ph.D. on October 11, 2007, all pending claims (1-4) were generally discussed in view of all of the applied prior art references (Kim et al. U.S. 2002/0025951 or WO 01/4794 in view of Berge et al.). An objection to the specification was also discussed. There was no agreement with respect to the claims. However, it was agreed that the objection to the specification would be overcome by amending page 2, line 2 (i.e., the first line of paragraph 8) by replacing "11 $\beta$ -substituted free amine (I)" with "11 $\beta$ -substituted free amine (I, see Chart A)," thereby making explicit reference in the specification to chart A. To be complete, a similar amendment was made to page 2, line 7 (i.e., line 6 of paragraph 8) by replacing "11 $\beta$ -substituted salts (II)" with "11 $\beta$ -substituted salts (II, see Chart A)." As discussed, those skilled in the art would recognize that the roman numerals (I and II) placed in parentheses after the generic name of the compounds in the specification at page 2 are referring to the compounds I and II identified in Chart A.

Although no agreement was made with respect to the claims, the Examiner's assistance in helping Applicant overcome the objection to the specification was greatly appreciated. Applicant also appreciated the opportunity to more fully understand the Examiner's position with respect to the obviousness rejection based on Kim et al. in view of Berge et al.

#### Objection To The Specification

It is believed that the objection to the specification has been overcome by the above amendments, for the reasons generally discussed above pertaining to the telephonic interview.

#### Rejection Under 35 U.S.C. §103(a)

Claims 1-4 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Kim et al. in view of Berge et al.

Applicant : Verlan H. VanRheenen  
Appln. No. : 10/815,351  
Page : 4

The reasons for the rejection are "those given in the previous Office Action."

In the previous Office Action (dated 3/02/07), the teachings of the prior art relied upon and the grounds for rejection were stated as follows:

Kim et al. teaches the instantly claimed compound, i.e., 17 $\alpha$ -acetoxy-21-methoxy-11 $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione and its antiprogestational properties (see US 2002/0025951, see sections 0001, 0005-0007, 0024,0028-0031 and Examples IX; WO 01/47945, see Abstract; page 20 and Figure 2, compound #11).

The instant claims differ from the reference by reciting specific salts, i.e., hydrochloride or hydrobromide salt thereof. However, the conversion of pharmaceutical agents into a salt form is routine in the pharmaceutical art. As discussed by Berge et al., the chemical, biological, physical and economic characteristics of medicinal agents can be manipulated and optimized by conversion to a salt form (see the entire article). Berge also teaches several commercially marketed salts, including the hydrochloride and hydrobromide salts that have FDA approval (see page 2, Table I). The claimed salts are *prima facie* obvious based on the teachings of the prior art and the level of skill of the ordinary artisan in the pharmaceutical art.

In reply to the rejection in the previous Office Action, Applicant explained that Kim et al. discloses nothing more relevant than the base compound (not a salt form), and that Berge et al. "provide evidence showing the difficulty involved in choosing the appropriate salt, and the unpredictability of the effect of choosing a particular salt form," and that development of an "appropriate salt form of any particular drug is a difficult, unpredictable endeavor involving more than routine experimentation."

In reply, the Examiner has stated, in the Final Rejection, that Applicant's arguments are unpersuasive because "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." *In re Keller*, 642 F.2d 413 (CCPA 1981) and *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986) are cited. This point of law has been taken out of its proper context as set forth in the cited case law, and has been misapplied to Applicant's arguments, which properly, in accordance with the law of *Graham v. John Deere*, 383 U.S. 1 (1966), discuss the scope and content of the prior art and ascertain the

differences between the claimed invention and the prior art to establish a factual background for the obviousness inquiry.

The CCPA in *Keller* stated that the Board of Patent Appeals and Interferences explained, in reaching their decision, that the test for determining whether it would have been obvious to substitute a digital timer for an analogue timer in a cardiac pacer disclosed in a primary reference, when the secondary reference discloses use of a digital timer in an analogous environment (a stimulator used in studies of the atrioventricular conduction system of a mammalian heart), “is not whether a suggestion to use digital timing in a cardiac pacer is found in Walsh [the secondary reference], but rather what Keller [the primary reference] in view of Walsh . . . would have suggested to one of ordinary skill in the art.” The CCPA, while affirming the Board’s decision, did so based on a finding that expert testimony submitted by the Applicant was accorded its due weight and did not effectively rebut the showing of *prima facie* obviousness. This can hardly be viewed as universal approval of what becomes an essentially meaningless expression when taken out of its proper context and misapplied.

The Federal Circuit Court of Appeals in *In re Merck & Co., Inc.* explained that an Applicant cannot effectively rebut a *prima facie* showing of obviousness by arguing that the concept of bioisosterism, as disclosed in one of the applied prior art references, could not be used to reliably predict the antidepressant properties of amitriptyline, based on the antidepressant properties of its bioisosteric equivalent imipramine, when other applied prior art references [i.e., Roche Reports] “expressly stated that amitriptyline was expected to resemble imipramine clinically in its depression alleviation effects.”

In the *In re Keller* case, the reference that was attacked for failing to suggest the use of a digital timer in a cardiac pacer was only being relied upon to show that digital timers were used in place of analogue timers in analogous environments, i.e., to show that digital timers were at least equivalent to analogue timers, not to show that it was known to use a digital timer in a cardiac pacer. In *Merck*, the reference that was attacked by the Applicant for failing to provide an expectation that amitriptyline would have antidepressant activity similar to the known antidepressant activity of its bioisosteric equivalent imipramine was only being relied upon to show structural similarity, while other references [the Merck Reports] were being used to establish an expectation of success.

When viewed in its proper context, the rule of *Keller and Merck*, which states that it is improper to attack references individually, is nothing more than an admonishment against attacking a reference for not teaching, suggesting, motivating or providing an expectation of success, when the rejection relies on another applied reference for that particular teaching, suggestion, motivation, or expectation of success.

When the proper context of the rule is understood, it can be seen that Applicant has not inappropriately attacked the individual references. Applicant has merely stated that neither of the applied prior art references teaches or suggests the claimed salts. The Examiner has not alleged that they do. To ascertain the scope and content of the prior art and to identify the differences between the claimed invention and the prior art does not constitute an improper attack on the prior art references individually.

The facts are that neither of the applied references teaches the claimed salts, neither of the applied references provides as much as a suggestion that the claimed salts of 19-norsteroids can be made, and neither of the references provides a disclosure of how the particularly claimed salts might be prepared.

Applicant appreciates that Kim et al. disclose the base compound, but are completely silent with respect to salt forms of the base compound. Applicant also appreciates that Berge et al. provides an overview of factors involved in identifying and screening potentially useful salts of pharmaceutically active compounds after they have been prepared, but only provides a very general statement that “[t]heoretically, every compound that exhibits acid or base characteristics can participate in salt formation.” Applicant also recognizes, as disclosed by Berge et al., that hydrochloride and hydrobromide salts of many pharmaceutically active base compounds are known. Applicant further concedes that salt forms often have many advantages over the free base form of a pharmaceutically active compound, and that there is often considerable motivation to discover suitable processes for crystallizing salt forms of particular pharmaceutically active base compounds.

However, even an intense desire for the claimed 17  $\alpha$ -acetoxy-21-methoxy-11 $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrochloride and/or hydrobromide salts coupled with possession of the base compound does not put the person of ordinary skill in the art in possession of the claimed salts, nor does it enable the person of

ordinary skill in the art to make the claimed salts. The references, alone or in combination, do not disclose a single example of how a hydrochloride or hydrobromide salt of any particular pharmaceutically active compound may be prepared. There is no evidence that any particular known technique for preparing a known hydrochloride or hydrobromide salt of any particular pharmaceutically active compound can be successfully employed for preparing the claimed 19-norsteroid salts. A cursory review of the relevant literature will reveal that in many cases it is not even possible to make a hydrochloride or hydrobromide salt form of a particular base compound that could theoretically be prepared. This is the reason that certain pharmaceutically active materials are sometimes prepared in other salt forms, such as maleates, sulfates, etc. Even in those cases where hydrochloride salts are now routinely prepared, different hydrochloride salts are prepared by different methods. In many, and perhaps most, of these cases, considerable insight, beyond that of the ordinary artisan, and/or considerable trial and error may be required to discover a successful method of preparing the particular hydrochloride and/or hydrobromide salt form. For example, it is disclosed, in "Handbook of Pharmaceutical Salts," P. Heinrich Stahl and Camille G. Wermuth, Helvetica Chimica Acta (2002), that fendiline hydrochloride (Sensit®) is prepared by dissolving freshly distilled 1,7-dihydro-1,3-dimethyl-7-[2-[(1-methyl-2-phenylethyl)amino]ethyl]-2H,6H-purine-2,6-dione in 96% ethanol, adding hydrogen chloride and hot water while cooling with ice-water, and precipitating, filtering and drying in vacuo at 100°C. This technique would not be useful for preparing the claimed 19-norsteroid salts. Generally, even when a particular salt form can be produced, considerable experimentation may be required to select the appropriate solvents or other dispersion systems, temperatures, cooling rates, etc. needed to precipitate or crystallize the desired product.

As disclosed by Kim et al., 21-substituted progesterones, including 19-norsteroids, have considerable utility and may be advantageously used to antagonize endogenous progesterone, induce menses, treat endometriosis, treat dysmenorrhea, treat endocrine hormone-dependent tumors, treat uterine fibroids, inhibit uterine endometrial proliferation, induce labor, and for contraception. As is evident from Berge et al., salt forms have many practical advantages. The rejection is based on an allegedly perceived benefit in providing the 19-norsteroids in a salt form. Surely, if preparing a salt form of a 19-norsteroid were a trivial

Applicant : Verlan H. VanRheenen  
Appln. No. : 10/815,351  
Page : 8

matter, Kim et al. would have disclosed such salts. Yet, despite a substantial perceived benefit, suitable 19-norsteroid salts were not known prior to Applicant's discovery of the claimed 17  $\alpha$ -acetoxy-21-methoxy-11  $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrochloride and hydrobromide salts. This discovery occurred approximately seven years after the Kim et al. invention was first published. A seven year lag between a perceived need for the 19-norsteroid salts and actual discovery of the salts is itself evidence of non-obviousness.

The invention satisfies a long-felt need. During the period between the discovery of Kim et al. and discovery of the claimed invention, it was not possible to market a commercially viable product due to the difficulty and expense associated with obtaining the base material at a suitable purity. By providing the 19-norsteroid compounds in a crystalline salt form, a purified product can be economically obtained, leading to commercial viability and great benefit to the public. Without applicant's discovery, the public may not have ever benefitted from the discovery of Kim et al.

The prior art does not provide any guidance on how to prepare the claimed hydrochloride and/or hydrobromide salts. Without such guidance, the person of ordinary skill in the art is merely left to contemplate her/his desire for the claimed 19-norsteroid salts. The ability to appreciate the desirability of things that do not yet exist, and may never exist, is ordinary, and does not place the person of ordinary skill in the art in possession of the object of desire.

The techniques for selecting or screening known salts for utility, as disclosed by Berge et al., does nothing toward placing the claimed invention in the possession of the person of ordinary skill in the art.

Applicant has discovered and disclosed appropriate techniques needed to obtain the claimed novel 19-norsteroid salts. Such techniques have not been previously disclosed and have not been shown to be obvious. Prior art that merely suggests the desirability of something that does not yet exist, without actually disclosing any method for obtaining the desired thing, is not enabling, and does not make the desired object obvious.

Finally, the Examiner has stated that *In re Williams*, 89 USPQ 396 (CCPA 1951) expresses a holding that salt forms of known compounds are *prima facie* obvious. Such

holding would be contrary to *Graham v. John Deere*, which requires that in every instance, obviousness must be determined based on the facts of the case, including the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any secondary considerations when they are present. In the *Williams* case, it was stated that the Examiner held as follows:

It is commonplace in chemistry that acids will react with the common alkali metal hydroxides, such as sodium or calcium hydroxide to form salts. Therefore the common salts are said to be unpatentable variants and to be suggested to the chemist by the old acid. No utility over the acid compound as it exists in nature apparently is found in the simple salts.

Initially, it should be noted that this is not the holding of the case, but that of the Examiner. The fact that the Board of Appeals affirmed the decision of the Examiner, and that the CCPA did not find any manifest error in the Board's decision, does not necessarily imply that either the Board of Appeals or the CCPA agreed with the Examiner's broad generalization regarding *per se* rules of obviousness. All that can be inferred is that the Board of Appeals and the CCPA agreed that calcium pantothenate is the unpatentable reaction product of pantothenic acid and calcium hydroxide.

The *per se* rule that claims to salts are *prima facie* obvious is not the holding in *In re Williams*, is inconsistent with *Graham v. John Deere*, and is inconsistent with the Examiner's rejection of the *Williams* application. Even the *Williams* Examiner limits the proposed *per se* rule to simple salts that are prepared by reacting an acid with an alkali metal hydroxide, and even then, only in those cases where the salt has no utility over the acid. The claims at issue are not directed to simple salts nor are they directed to the reaction product of an acid and an alkali metal hydroxide. Moreover, as implied by the Examiner, the claimed 19-norsteroid salts have considerably more utility than the base compound.

When a proper *Graham* analysis is applied, rather than the alleged rule of *In re Williams*, it is found that despite an urgent need for a suitable 19-norsteroid salt, such salts were not discovered until Applicant's discovery seven years after the 19-norsteroids of Kim et al. were disclosed. It is also found that the prior art does not provide any guidance as to how a person of ordinary skill in the art would go about preparing a 19-norsteroid salt. As may be

Applicant : Verlan H. VanRheenen  
Appln. No. : 10/815,351  
Page : 10

appreciated by reading Applicant's specification, the claimed salts cannot be obtained by merely adding a common alkali metal hydroxide, as was done in the *In re Williams* case. Rather, only a fairly select group of polar organic solvents have been found to be suitable for preparation of the desired salts. In addition, it has been found that particular concentrations of the free amine (about 0.1 to about 10 molar) and particular temperatures (about 20-25°C) are suitable for preparing the claimed salts.

Applicant understands that it is the Examiner's position that suitable methods for preparing hydrochloride and hydrobromide salts of 19-norsteroid compounds are well-known to those having ordinary skill in the art. Applicant respectfully disagrees, and submits that neither the applied prior art references, nor any other evidence of record, supports a finding that a person of ordinary skill in the art would expect any particular method known to be useful for preparing the hydrochloride or hydrobromide salt of any known pharmaceutically active base compound to be useful for preparing the claimed hydrochloride or hydrobromide 19-norsteroid salts. Thus, it is respectfully submitted that the prior art references do not provide disclosures sufficient to establish *prima facie* obviousness.

It is believed that upon further review, the Examiner will find that there is not any consistent methodology that may be employed in every instance for preparing a hydrochloride or hydrobromide salt of a pharmaceutically active base compound. To the contrary, in many instances it may be difficult, and in still other instances it may not even be possible.

#### CONCLUSION

In view of the above amendments and remarks, it is respectfully submitted that the application is in condition for allowance and notice of the same is earnestly solicited.

Respectfully submitted,

November 2, 2007

Date

/Gunter J. Evanina/

Gunther J. Evanina, Registration No. 35502  
Price, Heneveld, Cooper, DeWitt & Litton, LLP  
695 Kenmoor, S.E.  
Post Office Box 2567  
Grand Rapids, Michigan 49501  
(616) 949-9610

GJE/dac